Gut 1993; **34**: 994–998

CASE REPORTS

Isolated primary oesophageal involvement by lymphoma: a rare cause of dysphagia: two case histories and a review of other published data

B G Taal, P Van Heerde, R Somers

Abstract

Primary oesophageal involvement by lymphoma in two patients, one with Hodgkin's disease and one with non-Hodgkin's lymphoma is reported. In both, there were no manifestations of the disease outside the oesophagus, which is exceptionally rare. In the patient with non-Hodgkin's lymphoma, the oesophageal tumour was the first manifestation of lymphoma. Shortly after admission he developed a tracheo-oesophageal fistula from which he died before treatment could be started. In the patient with Hodgkin's disease, isolated oesophageal lymphoma was the first relapse after a 13 year interval free of disease. As he had previously received mediastinal irradiation he was treated with combination chemotherapy that resulted in long term survival (>five years). Several other long term survivors have been described but only after radiotherapy or surgery. These findings suggest that systemic chemotherapy may be equally successful in treating isolated primary oesophageal lymphoma, thus offering an alternative for those patients in whom local treatment is contraindicated.

(*Gut* 1993; **34**: 994–998)

The Netherlands Cancer Institute, Department of Medical Oncology, Amsterdam, The Netherlands
B G Taal
P Van Heerde
R Somers

Correspondence to:
B G Taal, MD, The Netherlands Cancer Institute, Department of Medical Oncology, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.

Accepted for publication 11 November 1992

Lymphomatous involvement of the oesophageal wall is rare. According to published studies, it is mainly associated with Hodgkin's disease, where it has been reported in up to 6% of cases in postmortem studies; the incidence of oesophageal invasion by non-Hodgkin's lymphoma does not exceed 1·6%.[1 2] Since 1935, only 90 cases of oesophageal lymphoma (53 Hodgkin's disease, 37 non-Hodgkin's lymphoma) have been described worldwide.[1–18]

In most patients, secondary involvement as a result of enlarged mediastinal lymph nodes was either shown or implied. Primary involvement, however, defined as lymphoma developing in the oesophageal wall itself, seems to be exceptionally rare, especially in its isolated form: we have been able to identify only six cases in which patients presented with oesophageal tumour as the only manifestation of lymphoma (five Hodgkin's disease, one non-Hodgkin's lymphoma).[2–4 8 16 17]

In this report we present two other patients from The Netherlands Cancer Institute with isolated primary oesophageal involvement by lymphoma. Their case histories show the diagnostic problems that may be associated with this disease.

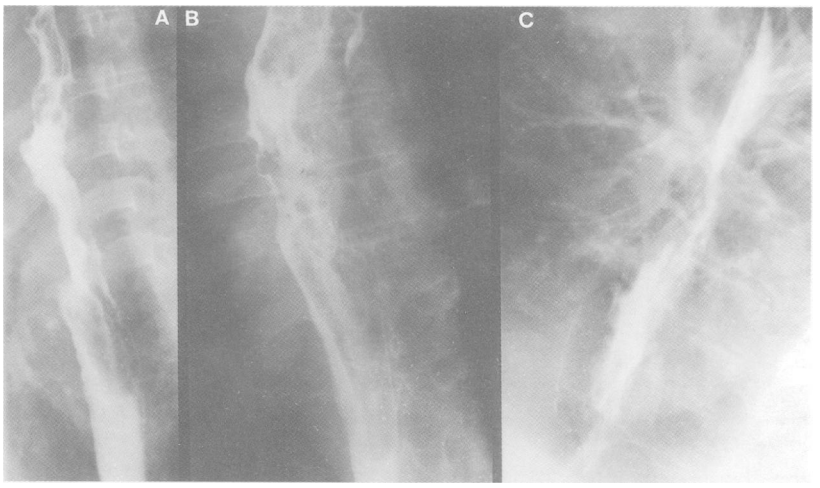

Figure 1: Case 1 (non-Hodgkin's lymphoma): barium swallow at presentation (A and B) showing irregular narrowing and ulceration of the oesophagus; shortly afterwards a broncho-oesophageal fistula developed (C).

Case 1

In September 1976 a 59 year old man was admitted to a local hospital for evaluation of intermittent complaints of retrosternal pain related to the ingestion of food, but sometimes also occurring at night. Barium swallow showed an irregular mucosal pattern in the midoesophagus. Endoscopy disclosed abnormal mucosa at 26 cm from the incisors; biopsies showed chronic inflammation.

While being evaluated for dysphagia he developed symptoms of intestinal obstruction with severe vomiting, caused by a large tumour in the sigmoid colon. A negative metastatic survey was followed by resection. Pathological examination showed a Dukes's C adenocarcinoma. The patient made an excellent recovery from this operation. Apart from relief of intestinal obstruction he also experienced relief of dysphagia that supported the hypothesis that oesophagitis had developed secondary to vomiting in the presence of large bowel obstruction.

He enjoyed good health until his initial complaints recurred one year later. Apart from retrosternal pain and discomfort there were also complaints of fatigue, anorexia, and intermittent

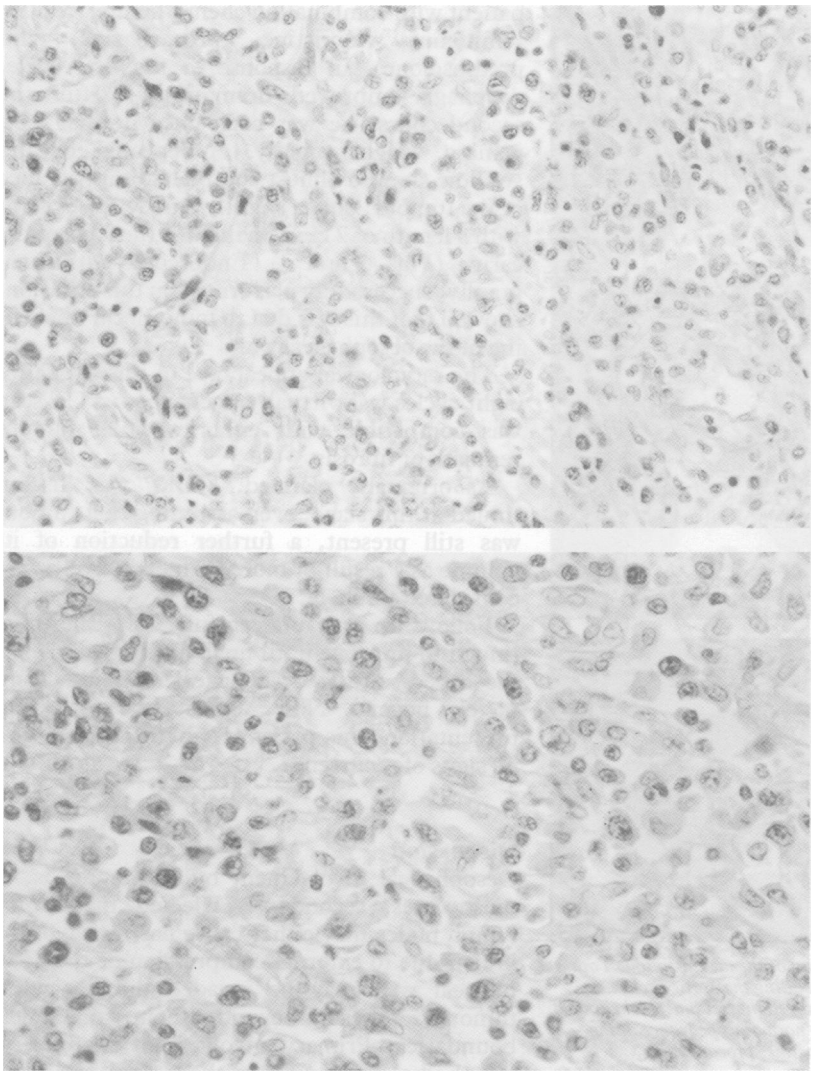

Figure 2: Case 1 (non-Hodgkin's lymphoma): malignant lymphoma, diffuse, predominantly small cleaved and centroblastic centrocytic; some plasmacytoid features. Haematoxylin and eosin; top originally ×250; bottom originally ×400.

fever. No abnormalities were found on clinical examination. Blood tests were normal with the exception of a slightly raised erythrocyte sedimentation rate. Barium swallow showed midoesophageal ulceration (Fig 1). Again, biopsies showed only chronic inflammation. Afterwards, oesophagoscopy was repeated twice as he failed to respond to conservative management. After a third attempt at oesophogoscopy in March 1978 a picture consistent with non-Hodgkin's lymphoma was found. The patient was referred to our hospital for further evaluation and treatment.

Endoscopy showed two small tumours at 21 cm from the incisors and a pedunculated polyp at 34 cm. Biopsies were positive for malignancy at both positions, defined as non-Hodgkin's lymphoma (Fig 2), mainly small cleaved according to the Working Formulation (1982), mainly centrocytic with the Kiel classification (1988). Routine staging procedures showed no manifestations of lymphoma outside the oesophagus, so a diagnosis of stage I extranodal non-Hodgkin's lymphoma was made. Radiotherapy was considered the best option for treatment but before this could be started, rapidly progressive dyspnoea developed. Bronchoscopy showed a narrowed left main bronchus apparently due to tumour compression. As an emergency measure, chemotherapy was applied (10 mg mitoxine, 2 mg vincristine, and 100 mg prednisolone). Further problems emerged the next day when a barium swallow (Fig 1) showed a broncho-oesophageal fistula, which was treated with antibiotics, a nasogastric tube for continuous suction, and a gastrostomy for feeding.

Further radiotherapy was cancelled, as the clinical condition of the patient deteriorated rapidly; he died from septic shock three weeks after admission. Necropsy disclosed malignant lymphoma in the distal 15 cm of the oesophagus associated with extensive fistula formation, mainly to the left main bronchus. Microscopy confirmed earlier findings. No manifestations of lymphoma were found outside the oesophagus.

Case 2

In June 1986, a 34 year old man presented with a three month history of progressive dysphagia and an associated weight loss of 10 kg. On admission he was unable to swallow anything but liquids and mashed solids. Thirteen years earlier he had been treated in our hospital for stage IIA nodular sclerosing Hodgkin's disease with pathological lymph nodes in the left supraclavicular region, both axillary regions, and the mediastinum. He was treated with irradiation: mantle field 40 Gy, submantle region 35 Gy, para-aortic region and spleen 40 Gy. A complete remission had been achieved; follow up was uneventful until current admission. Apart from dysphagia there were no complaints of night sweats, fever, or pruritus. A chest *x* ray film and physical examination were normal. Although erythrocyte sedimentation rate and alkaline phosphatase were slightly raised the other relevant laboratory values, including lactate dehydrogenase, were within normal limits.

Barium swallow showed severe stenosis of the distal oesophagus of about 8 cm in length associated with polypoid mucosal lesions. Computed tomography scanning showed malignant involvement of 12 cm of the oesophagus with infiltration of the aortic arch (Fig 3). Endoscopy showed a stricture with friable mucosa and ulceration, 7 cm long, at 28 cm from the incisors. Biopsies showed chronic inflammation but no evidence of malignancy. This was surprising: in our experience, patients with a history of mediastinal irradiation are at risk for developing a squamous cell carcinoma of the oesophagus and the clinical picture was highly suggestive of this type of malignancy. After repeated biopsies, evidence of malignancy was found. Contrary to our expectations, microscopy showed recurrent Hodgkin's disease. The mononuclear Hodgkin's cells and binuclear Sternberg Reed cells (Figs 4 and 5) showed the following immune marker pattern: CD 30 (syn BerH2, Ki1) and CD 15 (syn Leu m1) positive; LCA MT1, UCML1, L26, MB1, and MB2 negative. Staging bone marrow biopsy and CT scanning of the mediastinum showed no extraoesophageal manifestations of lymphoma. Endoscopic ultrasonography was attempted but the instrument could not be passed through the stenotic area.

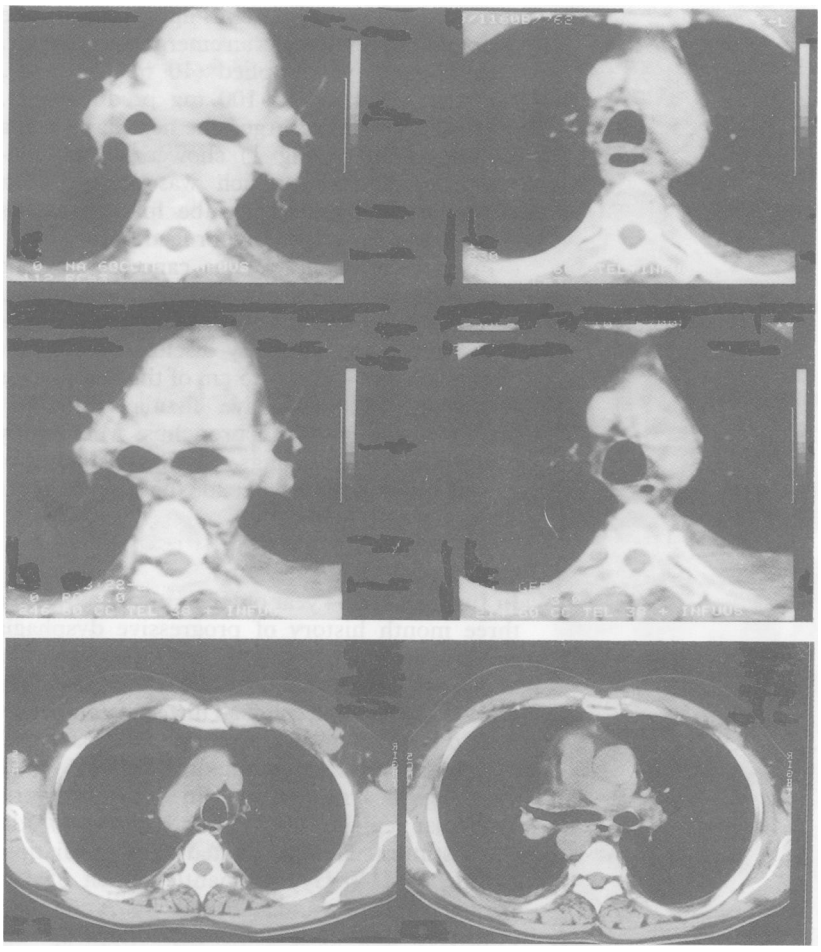

Figure 3: Case 2 (Hodgkin's disease): Computed tomography scan of the mediastinum. Top: at presentation showing a circular oesophageal tumour, possibly invading the aortic arch, no pathological lymph nodes. Middle: after 8×MOPP showing only slight residual thickening of the oesophageal wall at the level of the carina. Bottom: showing normal appearance of the oesophagus four years after diagnosis. MOPP=mitoxine, vincristine, procarbazine, prednisolone.

Based on these findings, extranodal recurrence of Hodgkin's disease, limited to the oesophageal wall, was considered to be the most likely diagnosis.

Radiotherapy was, at most, only a limited option in view of the dose applied to the mediastinal area in 1973. We decided to treat the patient with combination chemotherapy (MOPP =mitoxin, vincristine, procarbazine, and prednisolone). In response to the first cycle, dysphagia improved dramatically. After the second course he was back on a normal diet, gaining weight rapidly. A repeated barium swallow showed almost complete disappearance of the tumour; only a slightly narrowed segment with a length of 2 cm remained at the level of the carina (Figs 6 and 7). Endoscopic ultrasonography, successfully performed on this occasion, showed that this was due to minor local thickening of the oesophageal wall.

The radiological appearance of this area after eight cycles was virtually unchanged; a CT scan was compatible with either a small tumour remnant or fibrosis.

As originally planned, MOPP was discontinued at this stage; even assuming that tumour was still present, a further reduction of its volume as a result of more than eight cycles was considered unlikely.

Follow up was uneventful; CT scans continued to improve until finally, four years later, the aspect of the oesophageal wall was completely normal. Now, almost six years after presentation, this patient is alive and well with no signs of recurrence.

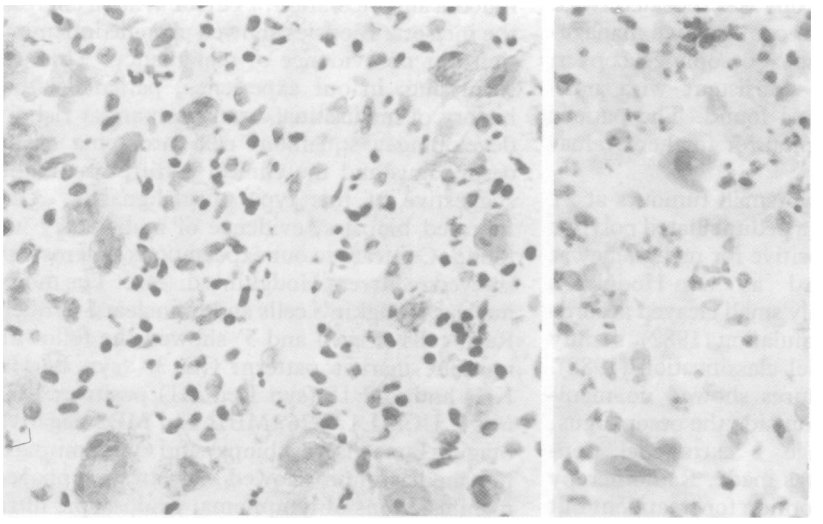

Figure 4: Case 2 (Hodgkin's disease): mononuclear Hodgkin's cells and binuclear Sternberg-Reed cells. Haematoxylin and eosin originally ×250.

Discussion

Oesophageal involvement by lymphoma is, in most cases, secondary. Affected mediastinal lymph nodes may either cause narrowing of the lumen due to external compression or the oesophageal wall may be invaded directly when tumours spread beyond their anatomical boundaries. Primary involvement, defined as lymphoma developing in the oesophageal wall itself, is rare, especially in its isolated form when it is the only focus of the disease.

Including our two patients, only eight cases of isolated primary oesophageal involvement by lymphoma have been published.[2-4 8 16 17] Tables I and II summarise their main characteristics.

As shown, recurrence of Hodgkin's disease, 10 or more years after initial treatment for this condition, was diagnosed in most cases. The nodular sclerosing form was the dominant histological sybtype, although this was not specified in all patients.

Isolated primary non-Hodgkin's lymphoma of the oesophagus seems to be exceptionally rare; in both reported cases, oesophageal lesions were the first manifestation of the disease. Presenting symptoms were not specific as neither patient initially complained of dysphagia.

An atypical presentation may contribute to a diagnostic delay, although this also occurred in patients with more specific symptoms. Diagnostic difficulties in those cases were related to confusing radiological and endoscopic appearances or failure to obtain histological confirmation of lymphoma.

A picture at barium swallow typical of malignancy, similar to that described in our case 2 patient, was only reported by Berman *et al.*[16] Other authors were confronted with a much more puzzling radiological picture, especially in early stages of the disease: a nodular aspect or

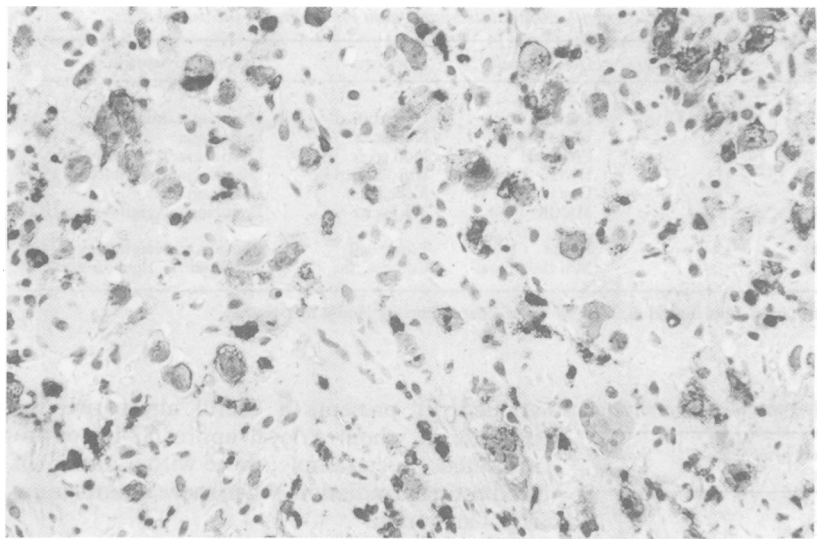

Figure 5: Case 2 (Hodgkin's disease): most of the atypical cells are reactive CD15 (Leu M1): membranous or cytoplasmic dark staining. Immunoperoxidase ×125.

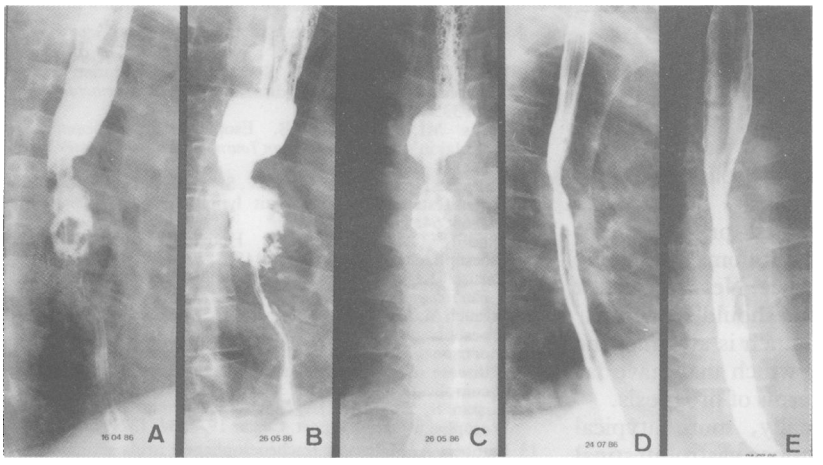

Figure 6: Case 2 (Hodgkin's disease): barium swallow at presentation (previous mediastinal irradiation for Hodgkin's disease stage IIA) showing irregular narrowing of the oesophagus and polypoid mucosal lesions, indicating carcinoma (A, B, and C). Considerable improvement after two cycles of MOPP (D and E). MOPP=mitoxine, vincristine, procarbazine, prednisolone.

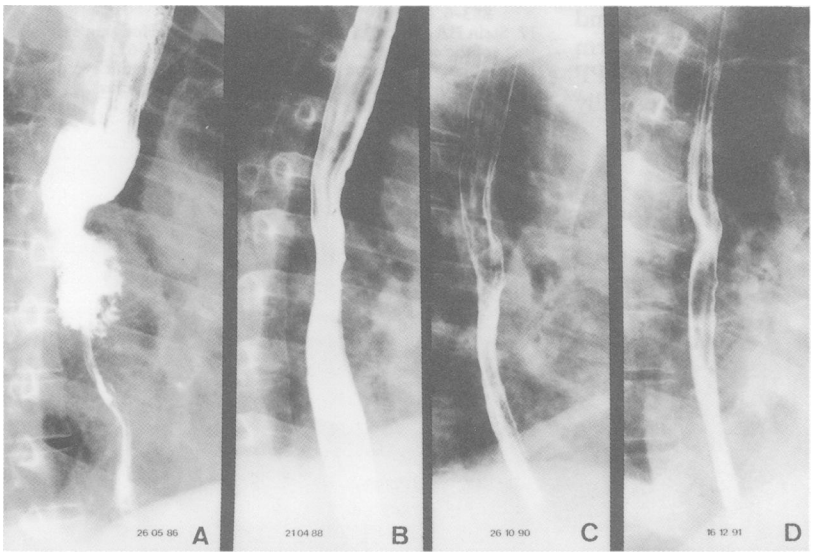

Figure 7: Case 2 (Hodgkin's disease): barium swallow at presentation (A), after two years (B), four years (C), and five (D) years; it shows only minor residual stenosis due to fibrosis.

irregular narrowing of the oesophagus due to submucosal tumours was mentioned most often and interpreted as either peptic stricture, radiation stricture, or external compression.[8 15]

Such interpretations seemed justified as all initial biopsies, with one exception,[4] were negative, indicating either no abnormalities or merely chronic inflammation. Eventually the correct diagnosis was made in seven patients after repeated endoscopic biopsies (case 1 and 2, Hambly and Blundell[8]), open biopsy[3] or examination or surgical specimens.[2 16 17]

Negative endoscopic biopsies can, to some extent, be explained by the specific growth pattern of the tumour; primary lymphoma arises in submucosal lymphoid patches, hence not within easy reach of biopsy forceps. Accessibility may improve when the tumour grows towards the oesophageal lumen, but matters become more complicated when growth is primarily directed in the opposite direction, towards the surface. Fistula formation – for example to the trachea – may then be the first sign of the true nature of the disease.

Radiological and endoscopic appearances are mainly dependent on the presence of intraluminal lesions. Submucosal swelling may be localised, circumferential, or multifocal, resembling benign conditions like fibrotic strictures, leiomyoma, achalasia, or varices. Polyps or papillomatous lesions may develop as a result of pronounced local proliferation. Such lesions are by no means unique and similar patterns may be found when other parts of the gastrointestinal tract are affected by lymphoma.[15]

Although difficult, an early diagnosis of primary oesophageal lymphoma seems to be vital as the response to treatment is often good. Table 2 shows that this is well documented for Hodgkin's disease. Four of the six patients survived five years; two of these four patients were still alive beyond that period, including our case 2 patient, the only long term survivor treated exclusively with combination chemotherapy.

Of the three patients that died, the cause of death was not mentioned in one case, a second patient died of oesophageal recurrence,[8] the third succumbed to systemic lymphoma five years after irradiation of a single oesophageal manifestation; local treatment had been completely successful, as indicated at necropsy, which failed to reveal any signs of malignancy in the oesophagus.[4] With the few data presently available, it is difficult to assess whether isolated primary involvement by non-Hodgkin's lymphoma would be equally responsive to treatment; our case 1 patient died of complications before any relevant treatment could be undertaken, whereas follow up in the case reported by Berman *et al*[16] was too short; only successful local excision of the tumour was reported although 'radiotherapy and chemotherapy were recommended to the patient'.

Long term survivors (six to nine years) after irradiation or chemotherapy have been described in patients in whom primary oesophageal non-Hodgkin's lymphoma was part of more widespread disease.[12 15] We have little reason to

TABLE I *Characteristics before treatment of patients (all men) with isolated malignant lymphoma of the oesophagus*

Author	*Age*	*Interval (y)*	*Oesophageal*	*Histology*	*Presenting symptoms*
Hodgkin's disease:					
Bichel[4]	21	1	Distal	Unspecified	Dysphagia, itching
Hambly and Blundell[8]	41	11	Middle	Nod scler	Dysphagia
Stein *et al*[17]	30	–	Proximal	Nod scler	Dysphagia, odynophagia†
Agha and Schnitzer[3]	28	11	Distal	Unspecified	Dysphagia, weight loss >15 kg
Wodzinski *et al*[2]	43	10	Distal	Mixed cell	Dysphagia
Case 2*	34	13	Middle	Nod scler	Dysphagia, weight loss >10 kg
Non-Hodgkin's lymphoma:					
Berman *et al*[16]	48	–	Distal	Large cell	Chest pain, weight loss >7 kg
Case 1*	59	–	Middle+distal	Centrocytic	Chest pain, fatigue, fever

*Present study; †odynophagia induced by alcohol ingestion. Nod scler=nodular sclerosing Hodgkin's disease.

TABLE II *Results of treatment in patients with isolated malignant lymphoma of the oesophagus*

Author	*Age (y)*	*Previous treatment*	*Treatment of oesophageal lymphoma*	*Survival (months)*
Hodgkin's disease:				
Bichel[4]	21	RT Axl Ln	RT+ 44 Gy	62
Hambly and Blundell[8]	41	RT Med Ln	RT	9
Stein *et al*[17]	30	–	Local excision, RT 40 Gy	>68
Agha and Schnitzer[3]	28	RT Med Ln	RT 22 Gy, CT†	60
Wodzinski *et al*[2]	43	CT†	Oesophagectomy, CT‡	>12
Case 2*	34	RT Med Ln	CT§	>60
Non-Hodgkin's lymphoma:				
Berman *et al*[16]	48	–	Local excision	?
Case 1*	59	–	None	1

*Present study; †3×MOPP (mitoxine, vincristine, procarbazine, prednisolone) and 3×MVPP (mitoxine, vinblastine, procarbazine, prednisolone); ‡ 6×EVAP (etoposide, vinblastine, doxorubicin, prednisolone); §8×MOPP; RT=radiotherapy; CT=chemotherapy; Axl=axillary; Ln=lymph nodes; Med=mediastinal.

assume that the response of solitary lesions would be fundamentally different.

Given the rarity of isolated primary oesophageal involvement by lymphoma, one may question its clinical significance. Nevertheless, it is our opinion that clinicians should be familiar with its clinical picture as much is at stake; the diagnosis is easily missed, which may have far reaching consequences in terms of prognosis.

Dysphagia or, occasionally, more atypical complaints related to the upper gastrointestinal tract developing in young patients with a history of lymphoma warrants suspicion, even in the absence of specific symptoms, enlarged lymph nodes, or a long disease free interval. Histological proof may be difficult to obtain but should be vigorously pursued.

Lacking sufficient data, specific advice about treatment cannot be given; both local and systemic approaches have resulted in long term survival. Our findings suggest that MOPP combination chemotherapy may be successfully applied. It presents a useful alternative for patients in whom a local approach is contraindicated – for example, those with a history of mediastinal irradiation, when more radiotherapy is not an option.

1 Trotman BW, Glick JM, de Barros SGS, Atkinson BF. Dysphagia in a patient with Hodgkin's disease. *JAMA* 1980; **244**: 2552–3.
2 Wodzinski MA, Gavalos M, Brown MJ, Thorpe JAC. Hodgkin's disease of the oesophagus. *Acta Haematol* 1988; **79**: 221–3.
3 Agha F, Schnitzer B. Esophageal involvement in lymphoma. *Am J Gastroenterol* 1985; **80**: 412–6.
4 Bichel J. Hodgkin's disease of the esophagus. *Acta Radiol* 1951; **35**: 371–2.
5 West WO, Bouroncle BA. Spontaneous perforation of the esophagus in Hodgkin's disease. *Am J Gastroenterol* 1960; **33**: 335–42.
6 Surks MI, Guttman AB. Esophageal involvement in Hodgkin's disease. *American Journal Digestive Diseases* 1966; **11**: 814–8.
7 Ehrlich AN, Stolder G, Geller W, Sherlock P. Gastrointestinal manifestations of malignant lymphoma. *Gastroenterology* 1968; **54**: 1115–21.
8 Hambly CK, Blundell JE. Hodgkin's disease of the oesophagus. *Australas Radiol* 1968; **12**: 43–8.
9 Caruso RD, Berk RN. Lymphoma of the esophagus. *Radiology* 1970; **95**: 381–2.
10 Strauch M, Martin Th, Remmeke W. Hodgkin's disease of the oesophagus. *Endoscopy* 1971; **3**: 207–9.
11 Morrison FS, Critz F, Tatum WT, Strauss HK. Hodgkin's disease of the oesophagus: sucessful treatment of a rare complication. *Cancer* 1973; **31**: 1244–6.
12 Nissan S, Bar-Moar JA, Levy E. Lymphosarcoma of the esophagus: a case report. *Cancer* 1974; **34**: 1321–3.
13 Lambert A. Malignant tracheoesophageal istula secondary to Hodgkin's disease. *J Thorac Cardiovasc Surg* 1975; **69**: 820–5.
14 Davis JA, Kantrowitz PA, Chandler HL, Schatzki SC. Reversible achalasia due to reticulumcell sarcoma. *N Engl J Med* 1975; **293**: 130–2.
15 Carnovale RL, Goldstein HM, Zornoza J, Dodd GD. Radiologic manifestations of esophageal lymphoma. *American Journal of Roentegenology, Radium Therapy and Nuclear Medicine* 1977; **128**: 751–4.
16 Berman MD, Falchuk KR, Trey C, Gramm HF. Primary histocytic lymphoma of the esophagus. *Dig Dig Sci* 1979; **24**: 883–6.
17 Stein HA, Murray D, Warner HA. Primary Hodgkin's disease of the esophagus. *Dig Dig Sci* 1981; **26**: 457–61.
18 Traube M, Waldron JA, McCallum RW. Systemic lymphoma initially presenting as an esophageal mass. *Am J Gastroenterol* 1982; **77**: 835–7.